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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,021	02/09/2005	Yoshiji Yamada	050070	3971

23850 7590 08/10/2007
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EXAMINER	
GREENE, JAIME M	
ART UNIT	**PAPER NUMBER**
1634	

MAIL DATE	DELIVERY MODE
08/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,021	YAMADA ET AL.	
	Examiner	Art Unit	
	Jaime M. Greene	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 6-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/23/05, 3/16/05, 2/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1 and 5, and polymorphisms 1, 3, and 4 in the reply filed on 7/12/07 is acknowledged. Currently, claims 1 and 5 and polymorphisms 1, 3, and 4 are under examination on the merits.

2. Claims 2-4, and 6-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/12/07.

Information Disclosure Statement

1. The information disclosure statements (IDS) were filed after the mailing dates on 8/23/05, 3/16/05, 2/9/05. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Note that lines were used to indicate corrections, and lines were drawn through references that were not considered.

Claim Rejections - 35 USC § 112 Written Description

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is broadly drawn to a method for detecting the genotype in a nucleic acid sample comprising analyzing the following polymorphisms: polymorphism at the base number position 3932 of the apolipoprotein E gene; polymorphism at the base number position -863 of the tumor necrosis factor-a gene; and polymorphism at the base number position 825 of G-protein 153 subunit gene

Claim 5 is broadly drawn to a method for diagnosing the risk of restenosis after coronary angioplasty, comprising the following steps (i) to (iii): (i) analyzing the polymorphisms selected from the group consisting of the following in a nucleic acid sample; (1) polymorphism at the base number position 3932 of the apolipoprotein E gene; (3) polymorphism at the base number position -863 of the tumor necrosis factor-.alpha. gene; and (4) polymorphism at the base number position 825 of G-protein .beta.3 subunit gene; (ii) determining, based on the information about polymorphism which was obtained in the step (i), the genotype of the nucleic acid sample; and (iii) assessing, based on the genotype determined, a genetic risk of restenosis after coronary angioplasty.

The rejected claims provides no structural limitation regarding what is encompassed by the terms "polymorphism at the base number position 3932 of the

apolipoprotein E gene", "polymorphism at the base number position -863 of the tumor necrosis factor-.alpha. gene", or "polymorphism at the base number position 825 of G-protein .beta.3 subunit gene".

When the claim is analyzed in light of the specification, the instant invention encompasses a method comprising the analysis of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to methods of analyzing polymorphisms selected from the group consisting of the following in a nucleic acid sample; (1) polymorphism at the base number position 3932 of the apolipoprotein E gene; (3) polymorphism at the base number position -863 of the tumor necrosis factor-.alpha. gene; and (4) polymorphism at the base number position 825 of G-protein .beta.3 subunit gene. The specification teaches SEQ ID NOs: 1, 3 and 4, which are sequences corresponding to the human genes that contain the claimed polymorphisms, however the specification does not further define the sequences for any other organisms nor does it teach if these same polymorphisms defined for human exist at all in other organisms. In addition, the specification does not provide guidance on the meaning of "nucleic acid sample", and therefore, said sample and said polymorphisms could be from any organism.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only sequences of the human

polymorphisms (SEQ ID NOs: 1, 3 and 4). The specification does not provide any characteristics that would allow one to identify any other homologous genes and polymorphisms from another organism or any particular portions or fragments or variants of the disclosed sequence that would allow for the genotyping of said polymorphisms or further for correlating those genotypes with restenosis. Furthermore, regarding polymorphisms in other organisms, there are, for example, 25 known Tnf SNPs in mice according the MGI (Mouse Genome Informatics. URL: http://www.informatics.jax.org/searches/snp_report.cgi?_Marker_key=25061). However, a search for mouse polymorphisms did not reveal any in mice that were stated to occur at position 863 in the mouse gene. Therefore, it is unclear whether or not there are polymorphisms at position 863 in the Tnf gene of mice or of other organisms, and it would be therefore, equally unclear to one of ordinary skill in the art what Applicant regards as those polymorphisms in all organisms for Tnf and similarly for Gnb3 and Apoe.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Also, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

In the instant application, with the exception of methods of analyzing polymorphisms selected from the group consisting of the following in a nucleic acid sample; (1) polymorphism at the base number position 3932 of the apolipoprotein E gene; (3) polymorphism at the base number position -863 of the tumor necrosis factor-.alpha. gene; and (4) polymorphism at the base number position 825 of G-protein .beta.3 subunit gene, and the SEQ ID NOs 1, 3 and 4 describing these polymorphisms in human, one of skill in the art cannot envision the detailed chemical structure of the aforementioned polymorphisms in all organisms. Adequate written description requires more than a mere statement that a polymorphism of the gene is part of the claimed invention and a qualitative description of the nature of the variant (e.g. a mutation is associated with diabetes). The nucleic acid itself is required.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is

claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The limited information provided regarding the sequences of the polymorphisms in humans is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of methods of analyzing polymorphisms selected from the group consisting of the following in a nucleic acid sample; (1) polymorphism at the base number position 3932 of the apolipoprotein E gene; (3) polymorphism at the base number position -863 of the tumor necrosis factor-.alpha. gene; and (4) polymorphism at the base number position 825 of G-protein .beta.3 subunit gene in all organisms besides those particularly disclosed in the specification at the time the application was filed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for claims 1 and 5.

Claim Rejections - 35 USC § 112 Enablement

5. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Teletronics Inc*, 8 USPQ2d 1217 (Fed Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986)) and *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)). These factors include the following:

The breadth of the claims and nature of the invention

Claim 5 is broadly drawn to a method for diagnosing the risk of restenosis after coronary angioplasty, comprising the following steps (i) to (iii): (i) analyzing the polymorphisms selected from the group consisting of the following in a nucleic acid sample; (1) polymorphism at the base number position 3932 of the apolipoprotein E gene; (3) polymorphism at the base number position -863 of the tumor necrosis factor-.alpha. gene; and (4) polymorphism at the base number position 825 of G-protein .beta.3 subunit gene; (ii) determining, based on the information about polymorphism which was obtained in the step (i), the genotype of the nucleic acid sample; and (iii) assessing, based on the genotype determined, a genetic risk of restenosis after coronary angioplasty.

The rejected claim encompasses analysis of any nucleic acid sample from any organisms for the elected polymorphisms.

The nature of the inventions not only involves determining the genotype of the elected polymorphisms but also correlating those genotypes with a risk for restenosis in all organisms. Since the locations of the polymorphisms in the genes are identified, the invention presumes that the polymorphisms are in the same locations in all organisms and that those polymorphisms are predictive for restenosis.

Guidance in the Specification and Working Examples

The specification teaches the sequences of the elected polymorphisms for the human genes and provides SEQ ID NOs 1, 3, and 4 to identify the human genes and polymorphisms in those genes.

The specification also describes (pages 58-65) a study in a population of Japanese 1313 men and 556 women that quantitates a correlation between specific gene sequences and restenosis in order to identify the risk of restenosis predicted by the presence of certain polymorphic sequences. With regard to the elected polymorphisms, the specification provides data that demonstrates an odds ratio of 7.33 as a predictor of risk of restenosis in Japanese men when the patient has a defined polymorphism in each gene. However, the specification does not provide information on how the odds ratio was determined. Specifically, although there are p-values regarding the correlation of each polymorphism with restenosis, the manner in which the applicants determined those p-values is not provided. For example, a significant p-value of 0.05 could indicate that the chance of a patient having one polymorphism and then restenosis is equal to or only slightly (51%) higher than the chance that the patient has the opposite polymorphism. Thereby, the odds ratio provides limited information

regarding the risk of a patient developing restenosis when that patient has polymorphisms at the base number position 3932 of the apolipoprotein E gene; at the base number position -863 of the tumor necrosis factor-alpha gene; and at the base number position 825 of G-protein beta 3 subunit gene.

In women, polymorphisms at the base number position 3932 of the apolipoprotein E gene and at the base number position -863 of the tumor necrosis factor-alpha gene were examined relative to their role in correlating with a risk for restenosis, however the polymorphism at the base number position 825 of G-protein .beta.3 subunit gene was not examined for its role in restenosis in women. Also, there is no corresponding risk factor result in women for the combination of polymorphisms at the base number position 3932 of the apolipoprotein E gene; at the base number position -863 of the tumor necrosis factor-alpha gene; and at the base number position 825 of G-protein beta 3 subunit gene.

The unpredictability of the art, the state of the prior art, level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a gene expression levels is high, the level of unpredictability in associating any particular expression of a particular gene or combination of genes with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied

three or more times, only 6 have been consistently replicated. Hirschhorn et al. suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn et al. caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a gene and a disease type (in this instance tumor detection).

Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract). Therefore the size of a population studied will effect the correlation of a gene expression to tumor detection.

Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, 18(24):20) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph).

Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

The specification only provides data from a single study, and the data is incomplete, in that it does not disclose the probability that a patient having the elected polymorphisms will develop restenosis. Also, the study is limited to Japanese men, and does not include data from other human populations or other organisms. Therefore, the information provided in the specification along with the prior and post filing art indicate that using polymorphisms to determine risk of restenosis is unpredictable.

The quantity of experimentation

Given the lack of guidance in the specification with regard to a transparent quantitative correlation between the elected polymorphisms and restenosis, the lack of study in populations aside from Japanese men, and the assessment in the art of the difficulties associated with using genes to predict susceptibility to complex disorders, the quantity of experimentation required to reach the conclusion of risk for developing restenois is extremely large. The skilled artisan would have to perform an extremely large study that included different populations and familial studies in a multitude of different organisms along with an extremely large amount of trial and error analysis to determine if in fact there is a way to predictably correlate the elected polymorphisms with risk of restenosis. Given the lack of guidance in the specification and the post filing

art with respect to accurately testing for genetic correlations with medical conditions, such analysis is replete with unpredictable experimentation and is considered undue.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Watanabe (Watanabe, et al. Thromb Haemost. 2001 Dec;86(6):1594-5.).

Watanabe teaches that thirty-five polymorphisms were analyzed in the study including APOE E3 and E4 (i.e. polymorphism at the base number position 3932); TNF -863C/A; and GNB3 825C/T (page 1594, column 1, paragraph 2, continued into column 2) (i.e. a method for detecting the genotype in a nucleic acid sample comprising analyzing the following polymorphisms: polymorphism at the base number position 3932 of the apolipoprotein E gene; polymorphism at the base number position -863 of the tumor necrosis factor-a gene; and polymorphism at the base number position 825 of G-protein 153 subunit gene).

Therefore all limitations of this claim have been taught by the reference.

8. Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Yamada (cited in IDS: Yamada, et al. N Engl J Med. 2002 Dec 12;347(24):1916-23).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Regarding claim 1, Yamada teaches a "screening study for 112 polymorphisms (page 1917, column 2, results section). Yamada teaches that "genotypes of the 112 polymorphisms were determined with a fluorescence- or colorimetry-based allele-specific DNA-primer-probe assay system (page 1917, column 1, "genotyping of polymorphisms" section), and that the polymorphisms examined included the polymorphisms for apolipoprotein E T3932C, G protein beta3 subunit C825T, and Tumor necrosis factor alpha C-863A (table 1) (i.e. a method for detecting the genotype in a nucleic acid sample comprising analyzing the following polymorphisms: polymorphism at the base number position 3932 of the apolipoprotein E gene; polymorphism at the base number position -863 of the tumor necrosis factor-a gene; and polymorphism at the base number position 825 of G-protein 153 subunit gene).

Therefore all limitations of claim 1 have been taught by the reference.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jaime M. Greene whose telephone number is 571-270-3052. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm; ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mary Mosher can be reached on 571-272-0906. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jaime M. Greene

JMG 5/18/07

/Sarae Bausch/
Patent Examiner, AU 1634